Angiopoietin-2: An Attractive Target for Improved Antiangiogenic Tumor Therapy
Damien Gerald, Sudhakar Chintharlapalli, Hellmut G. Augustin, and Laura E. Benjamin

Earlier Detection of Breast Cancer with Ultrasound Molecular Imaging in a Transgenic Mouse Model
Sanitha V. Bachawal, Kristin C. Jensen, Amelie M. Lutz, Sanjiv S. Gambhir, Francois Tranquart, Lu Tian, and Jurgen K. Willmann

G-protein Inactivator RGS6 Mediates Myocardial Cell Apoptosis and Cardiomyopathy Caused By Doxorubicin
Juanqi Yang, Biswanath Maity, Jie Huang, Zhan Gao, Adele Stewart, Robert M. Weiss, Mark E. Anderson, and Rory A. Fisher

Trp53 Inactivation in the Tumor Microenvironment Promotes Tumor Progression by Expanding the Immunosuppressive Lymphoid-like Stromal Network
Gang Guo, Luis Marrero, Paulo Rodriguez, Luis Del Valle, Augusto Ochoa, and Yan Cui

Therapeutic Efficacy of Bifunctional siRNA Combining TGF-β1 Silencing with RIG-I Activation in Pancreatic Cancer
Jonathan Ellermeier, Jiwu Wei, Peter Duewell, Sabine Hoves, Mareike R. Stieg, Tina Adunka, Daniel Noerenberg, Hans-Joachim Anders, Doris Mayr, Hendrik Poeck, Gunther Hartmann, Stefan Endres, and Max Schnurr

Precis: This important study suggests a rational approach to limiting the well-known cardiotoxic effects of doxorubicin (adriamycin), one of the most effective and widely used cytotoxic chemotherapy drugs for cancer treatment.

Precis: Findings reveal a previously unappreciated function for p53 in maintaining an immunological microenvironment that can suppress tumorigenesis and progression.

Precis: Vaccination of nasopharyngeal carcinoma patients targeting two pathogenic viral antigens produces potent immune responses after they have completed chemo/radiotherapy.

Precis: This study lays the foundation for the development of a novel ultrasound-based imaging approach for earlier detection of breast cancer and paves the way for translational clinical trials in the future.

Precis: New methods are offered to improve the identification of drug response biomarkers in cancer cells.

Precis: The potency of a therapeutic siRNA can be increased by a parallel strategy to combinatorially activate an RNA helicase that triggers inflammatory responses to double-stranded viral RNA, with implications for understanding how to reprogram the tumor microenvironment to destroy tumor cells.
LOX-Mediated Collagen Crosslinking Is Responsible for Fibrosis-Enhanced Metastasis
Thomas R. Cox, Demelza Bird, Ann-Marie Baker, Holly E. Barker, Melissa W-Y. Ho, Georgina Lang, and Janine T. Erler

**Précis:** The fibrotic status of a metastatic niche that is determined by the extracellular matrix plays a pivotal role in determining colonization of new sites by circulating tumor cells.

Evidence for a Role of the PD-1:PD-L1 Pathway in Immune Resistance of HPV-Associated Head and Neck Squamous Cell Carcinoma

**Précis:** HPV-associated oropharyngeal cancers, which are increasing in incidence in the developed world, evade immune surveillance through an escape pathway that is actively being targeted in clinical trials.

IFN-γ-Mediated Downregulation of LXA4 Is Necessary for the Maintenance of Nonresolving Inflammation and Papilloma Persistence
Chunhui Wang, Mingjie Xiao, Xiaoman Liu, Chen Ni, Jianhong Liu, Ulrike Erben, and Zhihai Qin

**Précis:** By helping resolve an inflammatory response, IFN-γ blockade can promote tumor regression by reprogramming the inflammatory microenvironment.

Myeloid-Specific Expression of Ron Receptor Kinase Promotes Prostate Tumor Growth
Devikala Gurusamy, Jerilyn K. Gray, Peterson Pathrose, Rishikesh M. Kulkarni, Fred D. Finkleman, and Susan E. Waltz

**Précis:** This study suggests a new strategy to treat prostate tumors, by blocking a tyrosine kinase that supports tumor-associated macrophages that drive immune escape.

HLA-Restricted CTL That Are Specific for the Immune Checkpoint Ligand PD-L1 Occur with High Frequency in Cancer Patients
Shamaila Munir, Gitte Holmen Andersen, Özcan Met, Marco Donia, Thomas Mørch Frøsig, Stine Kiaer Larsen, Tobias Wiernfeldt Klausen, Inge Marie Svane, and Mads Hald Andersen

**Précis:** PD-L1-specific cytotoxic T cells described for the first time in this study may be useful to harness for cancer immunotherapy to defeat mechanisms of immune escape used in various cancers mediated by the PD1 pathway.

A Chimeric Receptor with NKG2D Specificity Enhances Natural Killer Cell Activation and Killing of Tumor Cells
Yu-Hsiang Chang, John Connolly, Noriko Shimasaki, Kousaku Mihmura, Koji Kono, and Dario Campana

**Précis:** Findings illustrate how to increase the antitumor efficacy of NK cell therapy, a strategy that may be used to fight nearly any kind of human cancer.

Transcription Factor Y11 Contributes to Tumor Growth by Stabilizing Hypoxia Factor HIF-1α in a p53-Independent Manner

**Précis:** Findings suggest a mechanistic strategy to block a core hypoxia-driven progression pathway regardless of p53 status.

Arkadia Regulates Tumor Metastasis by Modulation of the TGF-β Pathway
Marco A. Briones-Orta, Laurence Levy, Chris D. Madsen, Debipriya Das, Yigit Erker, Erik Sahai, and Caroline S. Hill

**Précis:** An E3 ubiquitin ligase in the TGF-β signaling pathway is not required to regulate tumor growth but to colonize metastasis sites, suggesting novel antimetastatic strategies.

Phosphorylation of Ribosomal Protein S6 Attenuates DNA Damage and Tumor Suppression during Development of Pancreatic Cancer
Abed Khalaileh, Avigail Dreazen, Areej Khatib, Roy Apel, Avital Swisa, Norma Kidess-Bassir, Anirban Maitra, Oded Meyuhas, Yuval Dor, and Gideon Zamir

**Précis:** Findings reveal that a key mTOR effector molecule is crucial for initiation of K-Ras-induced pancreatic cancers, illuminating the centrality of this mTOR pathway to evade p53-mediated tumor suppression in this setting.
Dormant Cancer Cells Contribute to Residual Disease in a Model of Reversible Pancreatic Cancer

MicroRNA-Related Genetic Variants Associated with Clinical Outcomes in Early-Stage Non–Small Cell Lung Cancer Patients
Xia Pu, Jack A. Roth, Michelle A.T. Hildebrandt, Yuanqing Ye, Hua Wei, John D. Minna, Scott M. Lippman, and Xifeng Wu

Proliferation-Independent Control of Tumor Glycolysis by PDGFR-Mediated AKT Activation
Cong Ran, Huan Liu, Yasuyuki Hitoshi, and Mark A. Israel

Genetic Variation in Transforming Growth Factor Beta 1 and Mammographic Density in Singapore Chinese Women
Eunjung Lee, David Van den Berg, Chris Hsu, Giske Ursin, Woon-Puay Koh, Jian-Min Yuan, Daniel O. Stram, Mimi C. Yu, and Anna H. Wu

Telomere Length and Telomerase Activity Impact the UV Sensitivity Syndrome Xeroderma Pigmentosum C
Gerdine J. Stout and Maria A. Blasco

Identification of Inherited Genetic Variations Influencing Prognosis in Early-Onset Breast Cancer
Sajjad Rafiq, William Tapper, Andrew Collins, Sofia Khan, Ioannis Politopoulos, Sue Gerty, Carl Blomqvist, Fergus J. Couch, Heli Nevanlinna, Jianjun Liu, and Diana Eccles

xCT Inhibition Depletes CD44v-Expressing Tumor Cells That Are Resistant to EGFR-Targeted Therapy in Head and Neck Squamous Cell Carcinoma
Momoko Yoshikawa, Kenji Tsuchihashi, Takatsugu Ishimoto, Toshihumi Yae, Takeshi Motohara, Eiji Sugihara, Nobuyuki Onishi, Takashi Masuko, Kunio Yoshizawa, Shuichi Kawashiri, Makio Mukai, Seiji Asoda, Hiromasa Kawanu, Taneki Nakagawa, Hideyuki Saya, and Osamu Nagano

Focused Ultrasound Delivers Targeted Immune Cells to Metastatic Brain Tumors
Ryan Alkins, Alison Burgess, Milan Ganguly, Giulio Francia, Robert Kerbel, Winfried S. Wels, and Kullervo Hynynen

Caveolin-1–LRP6 Signaling Module Stimulates Aerobic Glycolysis in Prostate Cancer
Salahaldin A. Tahir, Guang Yang, Alexei Goltssov, Ki-Duk Song, Chengzheng Ren, Jianxiang Wang, Wenjun Chang, and Timothy C. Thompson

This study offers mechanistic insights into how aerobic glycolysis is increased in prostate cancer, possibly revealing critical targets for effective antimetabolic therapy in this setting.
Phenotypic Profiling of mTOR Complex 2 Is Involved in Alkaline Phosphatase ALPPL-2 Is a Novel Inhibitor of STAT3 Mixed Lineage Kinase MLK4 Is Involved in Tumorogenesis

Alkaline Phosphatase ALPPL-2 Is a Novel Inhibitor of STAT3 Homodimerization Selectively Suppresses STAT3 Activity and Malignant Transformation

Alkaline Phosphatase ALPPL-2 Is a Novel Pancreatic Carcinoma-Associated Protein

mTOR Complex 2 Is Involved in Regulation of Cbl-Dependent c-FLIP Degradation and Sensitivity of TRAIL-Induced Apoptosis

Phenotypic Profiling of DPYD Variations Relevant to 5-Fluorouracil Sensitivity Using Real-time Cellular Analysis and In Vitro Measurement of Enzyme Activity

Involvement of Lyn and the Atypical Kinase SgK269/PEAK1 in a Basal Cancer Signaling Pathway

Inhibition of PERK kinase, which controls the unfolded protein response (UPR), a near universally elevated process in cancer cells, was also found unexpectedly to affect amino acid metabolism, blood vessel density, and vascular perfusion in tumors.

Characterization of a Novel PERK Kinase Inhibitor with Antitumor and Antiangiogenic Activity

Notch and Wnt signaling pathways are critical oncogenic pathways in colorectal cancers that arise in humans.

This study addresses a rationale to target basal breast cancers, also known as triple negative breast cancers, which present a major clinical challenge due to their aggressive nature and lack of targeted treatments.

Findings of this study suggest a rational new target for anti-EMT therapy of cancer stem cells, perhaps relevant to many types of malignancy.

Findings show how mTORC2 stabilizes the FLIP apoptotic regulators, thereby connecting mTORC2 signaling to death receptor-mediated apoptosis.

Findings of this study suggest a rational new target for pan-EMT therapy of cancer stem cells, perhaps relevant to many types of malignancy.

Findings suggest a rationale to target basal breast cancers, also known as triple negative breast cancers, which present a major clinical challenge due to their aggressive nature and lack of targeted treatments.

Findings support the development of small molecule inhibitors of the kinase MLK4 to treat the significant number of KRAS-mutant colorectal cancers that arise in humans.

Findings of this study suggest a rational new target for anti-EMT therapy of cancer stem cells, perhaps relevant to many types of malignancy.
ABOUT THE COVER

Inactivation of the tumor suppressor p53 frequently occurs in tumors and tumor-associated stromal cells. This study shows that p53 dysfunction in tumor-associated stroma of B16F1 melanoma favors tumor establishment and progression by promoting an inflammatory microenvironment. Using immunofluorescence, it was found that lymphoid-like fibroblastic reticular cells, which express ER-TR7 (green), GP38 (red), and α-SMA (blue), were markedly expanded in the tumor microenvironment lacking functional p53. The expansion of this specialized stromal network was associated with augmented myeloid derived suppressor cells and angiogenesis. For details, see the article by Guo and colleagues on page 1668.